
Myocardial Tissue Fraction—Correction for Partial Volume Effects and Measure of Tissue Viability

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We have compared two independent methods of correcting the systematic underestimation in measurements of myocardial radiotracer concentration due to wall motion and small transmural wall thickness in cardiac PET studies. The first technique was based on measurement of the tissue fraction by fitting ^{15}O -labeled water dynamic PET data. The other technique involved the subtraction of the C^{15}O -blood volume scan from the transmission data, producing an image of extravascular density. In normal myocardial regions, both values were observed to be about 60% of myocardial tissue density. The tissue fraction was approximately 10% larger than the extravascular density in normal tissue regions. The ratio of α/D_{ev} indicates the proportion of the total extravascular tissue for a given ROI that is perfusable by water— independent of the partial volume effect. This ratio was confirmed to be the expected value in normal tissue regions but was reduced in regions of infarction. The use of ^{15}O -water, C^{15}O and transmission data may aid in the differentiation between perfusable and nonperfusable tissue in the infarcted myocardium.

J Nucl Med 1991; 32:2169–2175

Positron emission tomography (PET) is an imaging technique that enables accurate regional measurements of the concentration of radiotracers labeled with positron-emitting isotopes to be made in vivo. Such measurements are required for the quantification of the physiological and metabolic processes of interest following the administration of tracers employed in PET studies. The accuracy of the measurement of myocardial radiotracer concentration in cardiac PET studies is limited on account of the movement of the heart during the contractile cycle (1) and the small transmural thickness of the cardiac wall relative to the spatial resolution of PET scanners (2,3). These factors result in a systematic underestimation in the measurement of the true myocardial tissue radioactivity (the so-called

'partial volume effect' or PVE) and cause considerable bidirectional cross-contamination between the cardiac chambers and the myocardial tissue on the reconstructed tomographic images.

A number of techniques aimed at resolving these problems of underestimation of the true myocardial radioactivity have been previously proposed. Wisenberg et al. (2) estimated a correction factor for each myocardial segment by measuring the transmural wall thickness by two dimensional echocardiography. Henze et al. (3) developed a deconvolution technique to estimate the recovery coefficient based on the intrinsic spatial resolution of the PET scanner. Both methods were, however, limited because the effect of wall motion during the PET study was not taken into consideration. As the spatial resolution of PET devices continually improves, the relative contribution of cardiac wall motion to the underestimation of myocardial radiotracer concentration increases.

Iida et al. (1) have recently introduced the concept of tissue fraction (α) to solve the problem of underestimation of myocardial radioactivity, which has the additional advantage of eliminating errors introduced by cardiac wall motion. Tissue fraction was defined as the ratio of the mass of perfusable tissue within a given region of interest (ROI) to the volume of that ROI. This technique has been applied successfully to the measurement of absolute myocardial blood flow (MBF) (1), in which MBF was obtained as flow rate per mass of perfusable tissue excluding scar tissue (i.e., clearance MBF). The conventional MBF (flow rate per total volume of ROI including nonperfusable space, i.e., microsphere MBF) has also been calculated by multiplying the clearance MBF by the tissue fraction. The concept of tissue fraction has also successfully been applied for performing kinetic analysis to calculate [^{18}F]fluorodeoxyglucose (FDG) uptake in ischemic myocardium (4). Calculation of the tissue fraction was based on the measurement of the volume of distribution of water (V_d) from the ^{15}O -water dynamic data. V_d (the ratio of influx to efflux rate constants in the two compartment model describing the behavior of water in the myocardium) is directly proportional to the tissue fraction, with the constant of proportionality being the tissue-to-blood partition

Received Dec. 12, 1990; revision accepted June 4, 1991
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coefficient of water (p) (1,5). Therefore, by assuming a constant value of p [0.91 g/ml, based on in vitro water content data (6,7)] the value of tissue fraction for each ROI may be determined. Fixing the value of the partition coefficient in normal myocardial tissue is reasonable because the myocardial water content has been shown to be high (approximately 78%) with little variation (6). The regional variation of the partial volume effect would be greater compared with the uncertainty of the partition coefficient of water.

In the present study we have compared the implementation of partial volume correction by the tissue fraction technique with an alternative independent method that requires the subtraction of blood-volume from a normalized transmission image. The reconstructed transmission data gives an image of density (fractional mass in a given image volume element) which comprises both vascular and extravascular components. The blood-volume image, derived from the $C^{15}O$ scan, corresponds to the fractional component of the vascular space in a given volume element of the image. Subtraction of the blood-volume from the transmission image, which has been normalized to the density of blood (1.06 g/ml), provides a quantitative image of the "extravascular tissue density" (D_{ev}). This method, first reported by Rhodes et al. (8) for the lung, provides for a given ROI the ratio of the mass of extravascular tissue to the volume of that ROI. This should be equivalent to the degree of underestimation of the myocardial radioactivity in the corresponding ROI of an emission scan provided that the spatial resolution of both transmission and emission images are identical. This correction based on measurement of D_{ev} has been partially validated by phantom experiments (9).

In order to confirm the parity of the extravascular density and tissue fraction measurements, studies were performed in healthy volunteers and patients with nonreperfused myocardial infarction (Q-wave). We hypothesized that in the normal myocardium the values of α and D_{ev} should be approximately the same (i.e., $\alpha/D_{ev} \approx 1.0$). However, in instances of tissue necrosis (i.e., myocardial infarction), we expected a disparity in the tissue fraction and D_{ev} measurements (i.e., $\alpha/D_{ev} < 1.0$) because water should not exchange with infarcted tissue to a significant extent during the time course of the ^{15}O water measurement. D_{ev} , on the other hand, by virtue of the mode of its calculation, gives the anatomical tissue density and includes both perfusable and nonperfusable (i.e., scar) tissue components.

MATERIALS AND METHODS

Subjects

Studies were performed in nine healthy male volunteers (mean age 28 ± 5 yr, range 21–34 yr) and four patients with antecedent nonreperfused Q-wave myocardial infarction (2 males and 2 females, mean age 62, range 52–67). The area of asynergy was confirmed by two-dimensional echocardiography. All subjects

were studied at rest following a period of at least 6 hr fasting. All participants were informed of the investigational nature of these studies and written informed consent was obtained in each case. This protocol was approved by the Hammersmith Hospital Ethics Committee and the United Kingdom Administration of Radioactive Substances Advisory Committee (ARSAC).

PET

An ECAT 931-08/12 whole-body tomograph (CTI Inc., Knoxville, TN) was used in all the PET studies. This camera produces 15 cross-sectional tomographic images in an axial field of view (FOV) of 10.5 cm (10). All emission and transmission data were reconstructed using a Hanning filter with a cut-off frequency of 0.5 in units of the reciprocal of the sampling interval of the projection data (3.07 mm). This produced a similar spatial resolution in emission and transmission images (a transaxial spatial resolution of 8.4 ± 0.7 mm full-width at half-maximum (FWHM) at the centre of the FOV for emission images and 9.4 ± 0.7 mm FWHM in the transmission images). Hence, the recovery coefficient for small ideal structures was confirmed to be the same for both emission and transmission images.

All subjects were asked to lie supine on the scanner bed with their arms out of the FOV. The optimal imaging position was determined by a 5-min rectilinear scan following the exposure of an external ^{68}Ge ring source. A 20-min transmission scan was then performed by using the same ring source. These data were used to correct subsequent emission scans for tissue attenuation of the 511-keV annihilation gamma photons. At the end of the transmission scan, the blood-pool was imaged by the inhalation of ^{15}O -labeled carbon monoxide, which labels erythrocytes by the formation of carboxyhaemoglobin. The $C^{15}O$ inhalation lasted for 4 min (total subject dose of 6 GBq), and a 6-min single frame emission acquisition was initiated 1 min after the end of $C^{15}O$ inhalation. Venous blood samples were taken from a venflon cannula placed in an antecubital vein every minute during the scan, and the $C^{15}O$ concentration in whole blood was measured using a NaI well counter calibrated with the scanner.

After a 15-min period to allow for decay of the ^{15}O radioactivity in the body to background levels, myocardial blood flow was measured using a protocol previously validated in our laboratory (11). Briefly, $C^{15}O_2$ gas, which is converted in the lung to ^{15}O -labeled water (12) was inhaled for a period of 3.5 min (3–5 MBq/ml at a flow rate of 500 ml/min). A 25-frame dynamic PET scan was started 28 sec prior to the start of $C^{15}O_2$ delivery, thus enabling a measurement of background activity to be made. This lasted for a total of 7 min.

Data Analysis

All images were reconstructed on a MicroVax II computer using dedicated array processors employing standard reconstruction algorithms. Images were transferred to SUN 3/60 workstations for further analysis. Image manipulations were performed using the ANALYZE software package (Mayo Foundation, Rochester, MN). These procedures are described below.

Calculation of the Blood-Volume Image. The blood-volume image was calculated using the $C^{15}O$ scan data. The raw image was divided by the product of the average of the blood radioactivity concentration (cps/ml of whole blood) measured from the venous blood samples and the density of whole blood (1.06 g/ml). These images were also corrected to account for the decay

of ^{15}O during the 6-min acquisition period. The resultant quantitative images of blood-volume (V_B) have units of milliliters of blood-per-image volume element.

Calculation of the Extravascular Density Image. The reconstructed transmission data (Tr) were normalized on a pixel by pixel basis to the activity pixel counts in a region of interest (ROI) in the left ventricular chamber of the transmission image (Tr_{lvtroi}) and the density of blood (1.06 g/ml). The vascular components were subtracted from these images using the V_B images generated above. This procedure is summarized in Equation 1:

$$D_{ev} = 1.06 * ((Tr/Tr_{lvtroi}) - V_B) \quad \text{Eq. 1}$$

This resulted in quantitative images of extravascular tissue density (D_{ev}), which for a myocardial ROI is defined as the mass of extravascular myocardial tissue-per-volume element of ROI [g/ml_{roi}]. This technique has been previously validated for the measurement of lung tissue density (δ).

Designation of ROIs. ROIs were selected in the left ventricular chamber (as determined on the blood-volume images) and in three myocardial segments of the left ventricular wall, i.e., anterior, lateral, and septum. Positioning of tissue ROIs was performed by tracing ROIs on serial slices of the D_{ev} images. These tissue ROIs were projected onto the V_B , D_{ev} and dynamic ^{15}O water data sets. Values of V_B and D_{ev} for a particular anatomical tissue segment was determined as the mean of the values for each individual ROI drawn in that tissue segment. Tissue ROIs projected on the dynamic ^{15}O water data set were used to generate tissue time-activity curves. The average tissue time-activity curve for each anatomical segment was used for the fitting procedure for calculation of regional myocardial blood flow (MBF) and tissue fraction (*vide infra*). The arterial input function for this calculation was generated by projecting the left ventricular chamber ROIs onto the dynamic C^{15}O_2 data set.

Calculation of Tissue Fraction. Myocardial blood flow (f , flow rate per mass of perfusable tissue), tissue fraction (α), and the arterial blood volume fraction (V_a) were calculated for each myocardial segment according to the nonlinear least squares fitting technique of the tissue and the arterial ^{15}O -water time-activity curves reported previously (1,11). The following model equation was employed:

$$R(t) = \alpha \cdot f \cdot a(t) \otimes e^{-\frac{f}{p} \cdot t} + V_a \cdot a(t), \quad \text{Eq. 2}$$

where \otimes denotes the convolution integral, $R(t)$ is the C^{15}O_2 time-activity curve observed in the myocardial region, $a(t)$ is the true arterial blood input function, p is partition coefficient of water, and V_a is the contribution of radioactivity from the arterial blood-volume fraction in the myocardium and spillover activity from the left ventricular chamber. The time-activity curves, $R(t)$ and $a(t)$, were corrected for radioactive decay of ^{15}O .

A left ventricular time-activity curve $\{LV(t)\}$ was used to obtain the input function, $a(t)$, of ^{15}O -water to the myocardium. In order to minimize the statistical fluctuation in the left ventricle curve, relatively large left ventricular ROIs were drawn on the blood-volume image. The limited recovery in the left ventricular radioactivity measurement was corrected by assuming the left ventricular time-activity curve as:

$$LV(t) = \beta \cdot a(t) + (1 - \beta) \cdot f \cdot a(t) \otimes e^{-\frac{f}{p} \cdot t}, \quad \text{Eq. 3}$$

where β [ml/ml] is the recovery coefficient of the LV radioactivity concentration measured from the blood-volume image.

Solving Equations 2 and 3 gives

$$R(t) = \left(\frac{\alpha}{\beta} - \frac{(1 - \beta)}{\beta^2} V_a \right) \cdot f \cdot LV(t) \otimes e^{-\left(\frac{1}{p} + \frac{(1 - \beta)}{\beta}\right) \cdot f \cdot t} + \frac{V_a}{\beta} \cdot LV(t) \quad \text{Eq. 4}$$

and

$$a(t) = \frac{1}{\beta} \cdot LV(t) - \frac{(1 - \beta)}{\beta^2} \cdot f \cdot LV(t) \otimes e^{-\left(\frac{1}{p} + \frac{(1 - \beta)}{\beta}\right) \cdot f \cdot t} \quad \text{Eq. 5}$$

The values of f , α , and V_a were estimated by nonlinear least squares regression analysis and the value of β was fixed to that measured using the blood-volume scan. This technique has been previously confirmed to provide values of f , α , and V_a , which were consistent with those calculated using the arterial blood curve measured by a beta-probe as an input function (13).

Tissue Fraction to Extravascular Density Ratio, (α/D_{ev}). The definitions of tissue fraction (α) and the extravascular density (D_{ev}) are described by Equations 6 and 7, respectively:

$$\alpha = \frac{\text{Mass of } ^{15}\text{O}\text{-water perfusable tissue excluding arterial vascular component [g]}}{\text{Volume of ROI [ml]}} = \frac{\text{Mass of } ^{15}\text{O}\text{-water perfusable extravascular tissue plus venous component [g]}}{\text{Volume of ROI [ml]}} \quad \text{Eq. 6}$$

$$D_{ev} = \frac{\text{Mass of total extravascular tissue [g]}}{\text{Volume of ROI [ml]}} \quad \text{Eq. 7}$$

Therefore, calculation of the ratio of the tissue fraction to the extravascular density gives:

$$\frac{\alpha}{D_{ev}} = \frac{\text{Mass of } ^{15}\text{O}\text{-water perfusable extravascular tissue plus venous component [g]}}{\text{Mass of total extravascular tissue [g]}} \quad \text{Eq. 8}$$

For a given ROI, this ratio indicates the proportion of the extravascular tissue, which is capable of exchanging water and is independent of partial volume effects. By neglecting the vascular components, this ratio is expected to be approximately unity in viable (normal and/or ischemic but perfusable) tissue, as all the extravascular myocardial tissue should be capable of exchanging water. By assuming the venous vascular component to be 0.10 milliliters per gram of net myocardium (14), this ratio should be approximately 1.11. However, in regions of necrosis we would expect this ratio to be reduced as not all the tissue within the ROI would be perfusable, i.e., the fraction of the ROI which is occupied by scar tissue (included in the D_{ev} measurement) would not exchange water within the time frame of the ^{15}O -water measurement. This ratio would indicate the fraction of the residual perfusable tissue (and/or size of the scar tissue) in areas of infarction.

RESULTS

Typical transmission, blood-volume, and extravascular density images from a normal volunteer study are shown in Figure 1. A typical fit of the measured dynamic C^{15}O_2

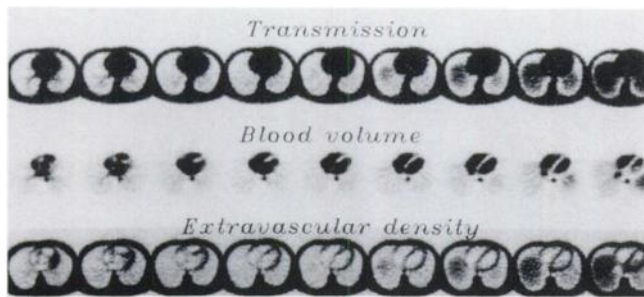


FIGURE 1. Axial transverse tomographic images of the density (top), blood density (middle), and extravascular density (bottom) obtained from a typical subject. Nine slices were displayed which were chosen from original 15 tomographic images.

data to the single tissue compartment model described by Equation 2 is shown in Figure 2.

Results obtained from the normal volunteer studies are summarized in Table 1. The average values of tissue fraction (mean \pm s.d.) for the lateral, anterior and septal walls were 0.71 ± 0.05 g/ml, 0.72 ± 0.09 g/ml, and 0.86 ± 0.08 g/ml, respectively. These values were significantly smaller than myocardial tissue density (1.04 g/ml) (difference was more than twice the standard deviation). Values of α in the septum were consistently higher than in the other segments. Myocardial blood flow was homogene-

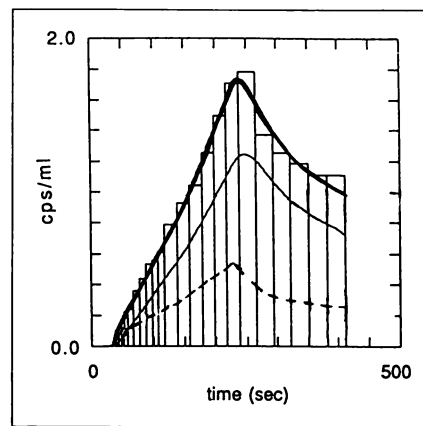


FIGURE 2. A fit of the model equation (Eq. 2) to the $C^{15}O_2$ time-activity curve obtained from a typical volunteer study (the lateral wall region of subject V2). Histograms correspond to measured data. The thin, solid line denotes the net myocardial curve (first term of Equation 2), the dashed line indicates the arterial blood component (second term of Equation 2), and the bold, solid line indicates the total concentration decay curve, $R(t)$. All curves were already corrected for radioactivity decay of ^{15}O .

ously distributed throughout all regions of the heart. The average value of MBF was 0.82 ± 0.15 ml/min per gram of perfusable tissue. For the same tissue ROIs, values of

TABLE 1

Summary of the Tissue Fraction (α), MBF(f), the Fitted Arterial Blood-Volume (V_a), the Total Blood-Volume (V_b), the Venous Vascular Component $\{(V_b - V_a)/\alpha\}$, the Extravascular Density (D_{ev}), and the ratio (α/D_{ev}) Obtained from Healthy Volunteer Studies

ROI	Subject No.									Mean	s.d.
	V1	V2	V3	V4	V5	V6	V7	V8	V9		
The tissue fraction, α (g/ml)											
LAT	0.67	0.82	0.74	0.65	0.66	0.68	0.67	0.76	0.71	0.71	0.05
ANT	0.71	0.86	0.64	0.57	0.73	0.85	0.70	0.81	0.64	0.72	0.09
SEP	0.94	0.91	0.71	0.89	0.94	0.81	0.94	0.84	0.77	0.86	0.08
MBF, f (ml/min/g)											
LAT	0.84	1.06	0.77	0.75	0.84	0.78	0.83	0.67	1.08	0.85	0.13
ANT	1.03	0.62	0.60	0.77	0.67	0.82	0.88	0.83	0.90	0.79	0.14
SEP	0.71	0.76	0.92	1.06	1.16	0.74	0.74	0.72	0.56	0.82	0.18
Arterial blood volume, V_a (ml/ml)											
LAT	0.14	0.17	0.23	0.29	0.39	0.23	0.32	0.18	0.05	0.22	0.10
ANT	0.18	0.30	0.34	0.38	0.04	0.21	0.28	0.17	0.17	0.23	0.10
SEP	0.06	0.20	0.41	0.04	0.04	0.28	0.06	0.25	0.29	0.18	0.13
Total blood volume, V_b (ml/ml)											
LAT	0.28	0.33	0.34	0.35	0.4	0.30	0.33	0.23	0.24	0.31	0.05
ANT	0.21	0.29	0.37	0.29	0.18	0.33	0.33	0.32	0.29	0.29	0.06
SEP	0.24	0.36	0.46	0.32	0.49	0.43	0.33	0.37	0.39	0.38	0.07
Venous vascular component, $(V_b - V_a)/\alpha$ (ml/g)											
LAT	0.21	0.20	0.14	0.09	0.02	0.11	0.01	0.07	0.28	0.12	0.08
ANT	0.04	-0.01	0.03	-0.16	0.19	0.14	0.07	0.19	0.20	0.08	0.11
SEP	0.19	0.17	0.08	0.32	0.48	0.18	0.28	0.15	0.13	0.22	0.11
Extravascular density, D_{ev} (g/ml)											
LAT	0.69	0.64	0.62	0.63	0.52	0.60	0.58	0.66	0.69	0.62	0.05
ANT	0.58	0.61	0.64	0.6	0.67	0.70	0.61	0.68	0.64	0.64	0.04
SEP	0.65	0.63	0.61	0.66	0.51	0.61	0.62	0.66	0.64	0.62	0.05
α/D_{ev} (g/g)											
LAT	0.97	1.29	1.20	1.03	1.27	1.14	1.15	1.16	1.03	1.14	0.10
ANT	1.21	1.42	1.00	0.95	1.10	1.21	1.14	1.19	1.00	1.14	0.13
SEP	1.44	1.45	1.15	1.36	1.85	1.34	1.53	1.28	1.20	1.40	0.19

V_a obtained from the ^{15}O -water data were systematically lower when compared with the blood volume, V_B , measured from the C^{15}O scan.

Values of D_{ev} were similar in all myocardial segments in a given subject. In the normal volunteer studies, values of D_{ev} were slightly (approximately 10%) smaller than α . The mean value of α/D_{ev} for the anterior and lateral walls were 1.14 ± 0.13 and 1.14 ± 0.10 g/g, respectively. In the septum, though, this ratio was consistently overestimated ($\alpha/D_{ev} = 1.40 \pm 0.19$ g/g).

Results from the patient studies are summarized in Table 2. Values of α , D_{ev} and consequently α/D_{ev} in regions of normal myocardium were consistent with the results from volunteer studies. However, the intra-subject regional variability in MBF was greater in this group compared with the normal volunteer group. It should be emphasized that the definition of MBF in this study was flow rate per viable tissue excluding nonperfusable space, i.e., clearance MBF.

In the infarcted regions, the calculated values of tissue fraction were systematically smaller than the extravascular density, and therefore, the ratios of α/D_{ev} were smaller than in normal regions. The mean value of D_{ev} in the infarcted regions was similar to that in normal myocardium but was more variable. Inspection of the data from each individual patient showed that in two cases D_{ev} was considerably reduced compared to control regions.

DISCUSSION

Two independent methods of correcting for the systematic underestimation in measurement of the myocardial radioactivity in cardiac PET studies have been compared.

Both quantities (the tissue fraction and extravascular density) were approximately equal and were substantially smaller than the density of the myocardium (approximately 1.04 g/ml). This indicates that rectification of the underestimation of myocardial radioactivity due to the partial volume effect and cardiac wall motion is essential for making quantitative measurements in cardiac PET studies. Furthermore, the error propagated to the calculated parameter of interest as a result of the error in the measured myocardial radioactivity is, in general, greater than the original error in the myocardial signal due to the nonlinear nature of tracer kinetic modeling procedures (15).

Slightly larger values of tissue fraction than extravascular density in normal regions can be explained as an effect of the inclusion of the venous blood-volume in the measurement of tissue fraction. As described in Equations 6 and 7, tissue fraction excludes only the arterial contribution, while the extravascular density excludes total blood-volume. The fraction of venous vascular component was expected to be 0.10 ml per gram of net myocardium based on a previous report and the assumption that the main contribution of the blood-volume was the venous component. The present study also provided a similar value for the venous vascular component. Since the total blood-volume (V_B) measured by C^{15}O and the arterial blood volume (V_a) obtained by H_2^{15}O fitting are related by

$$V_B = V_a + \alpha F_{vein}, \quad \text{Eq. 9}$$

where F_{vein} is the venous component. Hence, F_{vein} can be obtained as

$$F_{vein} = (V_B - V_a)/\alpha. \quad \text{Eq. 10}$$

Calculation of Equation 10 using our data (see Table 1) yielded values of the venous vascular component of 0.12 ± 0.08 and 0.08 ± 0.11 [ml/g] corresponding to the lateral and anterior regions, respectively. Thus, using a mean value of 0.10 ml/g, the ratio of α/D_{ev} would be expected to be approximately 1.11 (see Eq. 8). Agreement of this predicted value with our observed values of α/D_{ev} in normal regions (e.g., 1.14 ± 0.10 in the lateral and 1.14 ± 0.13 in the anterior wall region) provides an empirical validation of both the measurements—tissue fraction and extravascular density. The measurement of D_{ev} is, however, limited in the anterior wall region due to the close juxtaposition of the chest wall, which causes an overestimation in the measured D_{ev} due to spillover. In practice, though, this source of error does not seem to be great as the values of D_{ev} in normal subjects were homogeneous throughout all myocardial segments (Table 1).

The measurement of α is of limited accuracy in the septal region due to spillover of activity from the right ventricular chamber, as evidenced by the consistently raised values of α . The ^{15}O -water concentration in blood in the right heart is at the same concentration as in venous blood and is less than in the left ventricular chamber

TABLE 2

Summary of Tissue Fraction (α), MBF(f), Fitted Arterial Blood-Volume (V_a), C^{15}O -Blood-Volume (V_B), Extravascular Density (D_{ev}) and the Ratios (α/D_{ev}) Obtained from Patients with Previous Myocardial Infarction

ROI	Subject No.				Mean	s.d.
	P1	P2	P3	P4		
Tissue fraction, α (g/ml)						
Normal	0.81	0.80	0.81	0.74	0.79	0.03
Infarcted	0.64	0.19	0.36	0.58	0.44	0.16
MBF, f (ml/min/g)						
Normal	0.63	0.60	1.77	1.63	1.16	0.53
Infarcted	0.60	0.27	0.50	0.55	0.48	0.12
Arterial blood volume, V_a (ml/ml)						
Normal	0.15	0.23	0.06	0.29	0.18	0.10
Infarcted	0.50	0.18	0.03	0.22	0.23	0.10
Total blood volume, V_B (ml/ml)						
Normal	0.27	0.27	0.23	0.29	0.27	0.03
Infarcted	0.28	0.23	0.08	0.29	0.22	0.09
Extravascular density, D_{ev} (g/ml)						
Normal	0.72	0.69	0.66	0.69	0.69	0.02
Infarcted	0.79	0.30	0.92	0.57	0.64	0.25
α/D_{ev} (g/g)						
Normal	1.13	1.16	1.24	1.08	1.15	0.07
Infarcted	0.81	0.62	0.39	1.02	0.71	0.26

during $C^{15}O_2$ inhalation. The tracer kinetic model for calculation of myocardial blood flow treats venous blood as a tissue component due to the instantaneous equilibration of water in the heart (1,11). Consequently, spillover of right ventricular chamber activity into septal tissue ROIs will cause an overestimation in the measured value of α . This problem may be overcome by the use of alternative ^{15}O -water administration protocols such as slow intravenous infusions or bolus injections (1) of ^{15}O -water. Of these two alternatives, the latter requires independent measurement of the arterial blood radioactivity curve with arterial cannulation because of the high deadtime losses in the measured left ventricular time-activity curve found at the peak in bolus injection studies.

Both techniques are therefore of use as practical methods of partial volume correction in clinical cardiac PET studies, because of not requiring additional measurements using alternative imaging modalities such as two dimensional echocardiography, x-ray CT, or MRI scans. This would be a great advantage from the practical point of view.

However, it is the divergence of the measured values of α and D_{ev} that is of greatest significance. Such a disparity between the two measurements would most likely be due to the presence of necrotic myocardium. Such tissue is unlikely to exchange water during the time frame of the ^{15}O -water measurement. The D_{ev} measurement on the other hand includes both nonperfusable (e.g., scar) and perfusable tissue components and thus is dependent only on the physical dimensions of the myocardial wall and the ROI. It should be noted that in one case (P2) there was a marked reduction in the D_{ev} value in the infarcted region which may be due to decrease in the transmural myocardial wall thickness. Indeed, in this patient the wall thickness in the infarcted region was found to be half that of the normally contracting region by two-dimensional echocardiography.

Regions of interest positioned in the infarcted areas are likely to contain an admixture of both perfusable and nonperfusable scar tissue. Knowledge of the ratio of these two components represents clinically useful information. In fact, it has been demonstrated that this ratio is a useful predictor of the potential for recovery of asynergic myocardium following successful thrombolysis (16). For these reasons, we have interpreted the ratio α/D_{ev} as being a potential index of viability. Our original hypothesis on the values of residual tissue fraction, i.e., the α/D_{ev} ratio being close to unity in normal tissue and reduced in the infarcted region, have been confirmed. Thus, measurement of α/D_{ev} should aid in characterizing the pathologic myocardium in terms of its perfusable and nonperfusable components.

In all cardiac PET measurements, movement of the subject during the study can be one of the most important sources of error. A patient is required to maintain the same position during entire scan period, although this is

not always easy. Mismatch between the transmission and emission data may produce a serious error in the attenuation correction. In addition, movement can cause inadequate subtraction for the blood-pool from the transmission image in calculating the extravascular density image. It is, therefore, highly desirable to prepare a reliable fixation system for the subject to easily maintain the same position and/or to develop new sophisticated software algorithms that correct for movement. (This should be included in the attenuation correction process.)

Calculation of the tissue fraction was based on the following two assumptions: (1) the partition coefficient of water is equal to a ratio of known water content in myocardium to that in blood, and (2) the partition coefficient of water is constant even around the infarcted tissue. The first factor is based on the assumption that all the tissue water is freely exchangeable to the labeled water. This has been validated by our observation of consistency between observed and expected values of α/D_{ev} . However, concerning the second factor, the following questions still exist:

1. The nature of diffusion processes around necrotic tissue is unknown (but is probably limited), and therefore, the microscopic partition coefficient at the border zone may be different from normal myocardium. We would expect the microscopic partition coefficient to be larger in infarcted tissue on account of the unidirectional diffusion of water into scar tissue. The net effect would be an overestimation in the value of tissue fraction. The importance of this effect is equivocal as these diffusion processes are unlikely to occur to a significant extent during the time period of the ^{15}O -water measurement.
2. In the penumbra, surrounding sites of infarction, the microscopic flow distribution is probably not homogeneous, which is likely to produce a systematic underestimation in α as previously demonstrate (5, 15). Thus, the validity of using a fixed partition coefficient and the effects of flow heterogeneity in pathologic tissue should be evaluated further.

CONCLUSIONS

We have presented data on two independent methods to correct for underestimation of the measured myocardial radioactivity in cardiac PET studies. The consistency in the results suggests that both methods are suitable for the correction of losses due to the partial volume effect and cardiac wall motion. Further validation studies to examine the ability to quantify absolute myocardial radiotracer concentrations using these two approaches should be performed. The use of these two methods has widespread applications in quantitative cardiac parametric imaging using PET. The measured value of D_{ev} is dependent only on the physical dimensions of the heart wall and the size of the ROI whereas the value of α is additionally dependent

on physiological properties of the myocardial tissue contained within the ROI, i.e., the ability to exchange water. This explains the divergence of the two values in infarcted myocardium. The residual tissue fraction (α/D_{ev}) is a quantitative index of the proportion of perfusable tissue within a region of functionally impaired myocardium. This may be a clinically important parameter and further studies to this end are required.

ACKNOWLEDGMENTS

We are greatly indebted to the staff of MRC Cyclotron Unit, Hammersmith Hospital London, U.K., in particular, Miss Claire J.V. Taylor and Mr. Graham Lewington for technical support, and Drs. Peter Bloomfield, John Ashburner, and Jon D. Heather for lending the computer assistance. This work was in part supported by a grant from the Japanese Heart Foundation & Bayer Yakuhin. RDS is a recipient of a Medical Council Postgraduate Studentship from King's College. This work was presented in part at the 37th Annual Meeting of the Society of Nuclear Medicine, St. Louis, MO, 1990.

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